Determinants of T2* relaxation in white matter: insights from postmortem analyses

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1. Introduction

T2* weighted gradient echo images can show considerable variations of signal intensity between different white matter structures of the brain [1]. As T2* tissue contrast increases with higher field strength, the contribution of microstructural components with different magnetic susceptibility has been discussed including myelin and its orientation relative to B_0 as well as the paramagnetic effect of iron [2-4]. In this context, R2* relaxometry (R2*=1/T2*) has been proven as a sensitive and linear means to assess brain iron concentrations in white matter [5]. However, it remains unclear why the sensitivity of R2* for iron in white matter is substantially smaller than in gray matter. Therefore, the goal of this study was to investigate possible contributions of iron deposition, myelin density and fiber orientation on R2* relaxation rates in white matter by using quantitative MRI of postmortem brains in situ and by assessing regional iron concentrations with inductively coupled plasma mass spectrometry.

2. Subjects and Methods

Ten deceased subjects (age at death: 38-81years) without a history of neurologic disorder or trauma underwent in situ MRI at 3T (TimTrio, Siemens, Erlangen, Germany) within 72 hours after death. Brain temperature at the start of the scan was between 4 ° and 24 °C. R2* relaxation data was acquired with a 3D gradient echo sequence (TR/TE/FA = 68 ms/4.92 ms/20°, resolution=1x1x4 mm³) with 12 equally spaced echoes (spacing = 4.92 ms). R2* relaxation rates were calculated by fitting a mono-exponential decay function and by considering noise with a truncation model [6]. Magnetization transfer ratio (MTR) was used to semi-quantitatively assess the impact of myelin density [7]. MTR data was acquired with a 3D gradient echo sequence (TR/TE/FA = 40 ms/7.38 ms/15°, resolution = 1x1x4 mm³) performed with and without Gaussian shaped saturation pre-pulses. To study the effect of fiber orientation relative to B_0, diffusion tensor imaging (DTI) data was obtained with a diffusion weighted spin echo EPI sequence (TR/TE = 6.7 s/95 ms, 12 directions). A higher *b*-value of 2000 s/mm^2 was applied to account for reduced diffusivity in cooled tissue [8]. DTI image analysis included only regions with a fractional anisotropy greater than 0.3 and focused on the orientation of the principal diffusion direction relative to B_0.

After MRI, brains were extracted and fixed in 4% neutral buffered formalin for a minimum of three weeks. Tissue specimens were taken from various white matter structures (body of corpus callosum, frontal, temporal, and occipital white matter). Iron concentration in the specimens were determined with an inductively coupled plasma mass spectrometer (Agilent 7500ce, Agilent, Waldbronn, Germany) at m/z 56 in He-mode. According to the position of the dissected tissue specimens, regions of interest were outlined and affinely transformed to R2*, MTR and DTI data. Univariate and multiple regression analyses served to investigate possible contributions of myelin density, fiber orientation, and chemical determined iron concentration to R2* relaxation rates.

3. Results

Univariate linear regression analyses revealed significant correlations of R2* with iron concentration (r=0.34, p<0.001) as well as with MTR (r=0.43, p<0.001), but not with the underlying fiber orientation (r=0.03, p=0.65). Corresponding scatter plots are shown in Figure 1. When including all parameters in a multivariate regression model, both, iron concentration (beta=0.37) and MTR (beta=0.46) remained as independent predictors of R2* in white matter.

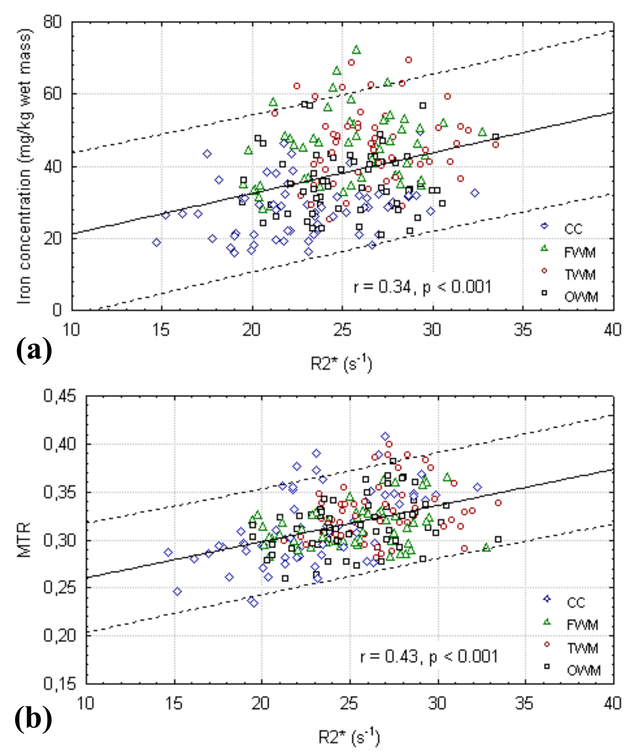

Figure 1: Correlations of R2* with iron concentration (a) and with magnetization transfer ratio (b).

4. Discussion and Conclusion

Our results suggest that the density and possibly also the structure of myelin is the dominant determinant of R2* in white matter while the presence of iron additionally has a strong effect. These results argue that the paramagnetic susceptibility of brain iron is counteracted by the diamagnetic susceptibility of the myelin lipids which may well explain the reduced sensitivity of R2* for iron mapping in white matter. Our results do not support the hypothesis that fiber orientation contributes to the phenomenon of T2* relaxation.

References:

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